The specification is amended on page 6 to recite "(SEQ ID NO: 7)" in order to identify the SEQ ID NO. of the DNA sequence.

Claim 1 is amended to recite "A recombinant antibody product, comprising the V_H domain of the OKT3 antibody, wherein the cysteine at position H100A of said V_H domain is substituted with a polar amino acid , wherein said position H100A is according to the Kabat numbering system". Support for the amendment is found, for example, at page 2, lines 9-14.

Claim 2 is amended to recite "The recombinant antibody product". Support for the amendment is found, for example, at page 2, lines 9-14 and Claims 1 and 2 as originally filed.

Claim 3 is amended to recite "comprising the amino acid sequence depicted by SEQ ID NO: 2". Support for the amendment is found, for example, at page 5, lines 15-16.

Claim 4 is amended to recite "A method for the production of the recombinant antibody product according to any one of claims 1 to 3, characterized by the steps of: a) obtaining mRNA from freshly subcloned hybridoma cells of OKT3 and transcription into cDNA, b) amplifying the DNA coding for the variable domains of the light and heavy chains by means of PCR, c) cloning of the DNA obtained in b) into a vector adapted for site-specific mutagenesis as well as introduction of a mutation in said position H100A of said VH domain, wherein said position H100A is according to the Kabat numbering system, wherein said mutation is the substitution of a cysteine with a polar amino acid, and d) inserting the mutated DNA obtained in c) in an expression vector and expression in a suitable expression system." Support for the amendment is found, for example, in Claim 4 as originally filed.

Claims 6-9 are amended to in order that Claims 6-9 depend only from Claim 4. Support for the amendment is found, for example, in Claims 6-9 as originally filed.

Claim 7 is amended to recite "said cloning uses a primer comprising the sequence depicted by SEQ ID NO: 7". Support for the amendment is found, for example, in page 3, line 12.

New Claims 12-22 are supported by Claims 3-9 as originally filed.

New Claim 23 is supported by page 5, lines 15-16.

New Claim 24 is supported by page 2, lines 4-6 and page 5, lines 15-16.

New Claim 25 is supported by page 4, lines 24-26.

New Claim 26 is supported by page 4, lines 11-13.

New Claim 27 is supported by page 4, lines 11-19 and 24-26, and page 5, lines 15-16.

No new matter is added in any of the above amendment and the Examiner is respectfully requested to enter the amendments and reconsider the application.

The Response

1. Objection to specification

The Examiner objects to the lack of a first sentence claiming priority to a prior application. Applicants have amended the specification by inserting a sentence to the beginning of the specification to indicate priority claimed to International Application No. PCT/DE98/01409, filed May 22, 1998, and German Patent Application No. 187 21 700.1, filed May 23, 1997. Therefore, in view of the amendment, the Examiner's objection should be withdrawn.

The Examiner objects to the alleged lack of an abstract. Applicants traverse this objection. Applicants respectively point out that page 10 contains a separate sheet upon which is the abstract of the disclosure. Therefore, the Examiner's objection should be withdrawn.

The Examiner objects to the lack of a SEQ ID NO. on page 6, line 18. Applicants have amended the specification by inserting a SEQ ID NO. to identify the DNA sequence. Therefore, in view of the amendment, the Examiner's objection should be withdrawn.

The Examiner objects to the specification in that the address of the American Type Culture Collection is not current. Applicants have amended the specification by replacing the disclosed address with the current address. Therefore, in view of the amendment, the Examiner's objection should be withdrawn.

The Examiner objects to the phrase "by means of PCR" in Claim 4. Applicants traverse this objection in that "amplifying [a DNA] by means of PCR is not atypical claim

language. PCR is a well-known molecular biology technique to one of ordinary skill of the art, and it is clear and definite that the amplifying of the DNA is by the technique of PCR. Therefore, the Examiner's objection should be withdrawn.

The Examiner objects to Claims 4-9 as being in improper form because a multiple dependent claim cannot depend from a multiple dependent claim. Applicants have amended these claims so that no multiple dependent claim depends from a multiple dependent claim. Therefore, in view of the amendments, the Examiner's objection should be withdrawn.

The Examiner objects to Claims 1, 3, 5, and 7 for failing to recite the SEQ ID NOs. Applicants have amended Claims 3 and 7 to recite the appropriate SEQ ID NOs. The term "OKT3" is a proper noun of a specific "monoclonal IgG 2a-type antibody originating from mice, which recognizes an epitope of an ε-subunit of the human CD3 complex" and the hybridoma which produces OKT3 is deposited with American Type Culture Collection (page 1, lines 5-16). Claim 5 recites the primers of Bi5, Bi8, Bi4 and Bi3f. "Bi5", "Bi8", "Bi4", and "Bi3f" specifically denote a specific primers of specific sequences known to one skilled in the art as described in Dübel, et al. (*J. Immunol. Meth.* 175:89-95, 1994) and Gotter, et al. (*Tumor Targeting* 1:107-114, 1995) (page 2, lines 15-32). Therefore, in view of the amendment, the Examiner's objection should be withdrawn.

2. 35 U.S.C. § 112, second paragraph rejections.

The Examiner rejects Claims 1-9 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The rejection of Claims 1-9 is traversed in part and overcome in part in view of the amendments.

A) The Examiner rejects Claims 1-9 in that allegedly the term "OKT3" is a trademark or trade name. Applicants respectfully traverse this basis of rejection. The term "OKT3" is not a trademark or trade name. The term "OKT3" is a proper noun of a specific "monoclonal IgG

2a-type antibody originating from mice, which recognizes an epitope of an ε-subunit of the human CD3 complex" (page 1, lines 5-7). Therefore amended Claims 1-9 are clear and definite.

B) The Examiner rejects Claims 1-9 in that allegedly the phrase "position H100A of the OKT3 antibody" is indefinite in that the disclosure does not provide a numbered reference sequence and that the term "OKT3" is a trademark. Applicants respectfully traverse this basis of rejection in part and avoid the rejection by amendment in part. For the reasons given above, the term "OKT3" is not a trademark. Amended Claim 1 recites "wherein said position H100A is according to the Kabat numbering system". Therefore amended Claims 1-9 are clear and definite.

C) The Examiner rejects Claim 1-9 in that allegedly that it is unclear if position H100A of the OKT3's antibody has the cysteine to serine exchange on one or both heavy chains. Amended Claim 1 recites "the V_H domain of the OKT3 antibody, wherein the cysteine at position H100A of said V_H domain is substituted with a polar amino acid". It is clear that the position H100A relates to only one V_H domain. Therefore amended Claim 1 is clear and definite.

D) The Examiner rejects Claims 2 and 3 in that allegedly there is insufficient antecedent basis for "The monoclonal antibody" and "the polar amino acid". Amended Claim 1 recites "A recombinant antibody product" while amended Claims 2 and 3, which depend from Claim 1, recite "The recombinant antibody product". There is antecedent support for "The recombinant antibody product" in Claim 1. Amended Claim 1 recites "a polar amino acid" while amended Claim 2, which depends from Claim 1, recites "the polar amino acid". There is antecedent support for "the polar amino acid" in Claim 1. Therefore amended Claims 2 and 3 are clear and definite.

E) The Examiner rejects Claims 4-9 in that allegedly there are essential steps missing from Claims 4-9 needed for the production of the monoclonal antibodies of any of Claims 1-3.

Amended Claim 4, from which Claims 5-9 depend from, recites the production of a "recombinant antibody product". Since a single-chain Fv is sufficient to constitute a "recombinant antibody product", the claimed method is clear and definite in the describing a method to produce a "recombinant antibody product". Therefore amended Claims 4-9 are clear and definite.

F) The Examiner rejects Claims 4 and 6-9 in that allegedly the term "suitable primers" is indefinite. Amended Claim 4 has the term "suitable primers" deleted. Claims 6-9 depend from Claim 4 and do not recite "suitable primers". Therefore amended Claims 4 and 6-9 are clear and definite.

G) The Examiner rejects Claims 4-9 in that allegedly the term "the desired mutation" is indefinite. Amended Claim 4 has the term "the desired mutation" deleted. Claims 5-9 depend from Claim 4 and do not recite "the desired mutation". Therefore amended Claims 4-9 are clear and definite.

H) The Examiner rejects Claims 8 and 9 in that allegedly the term "pHOG21" is indefinite because the characteristics of "pHOG21" are not known. Applicants respectfully traverse this basis of rejection. The term "pHOG21" specifically denotes a distinct plasmid as described in Figure 1 (page 4, line 32 to page 5, line 14). In addition, Kiripyanov, et al. (*J. Immunol. Meth.* 196:51-62, 1996) describes pHOG21 on Figure 1 (cited on page 3, lines 25-27), and Kiripyanov, et al. (*J. Immunol. Meth.* 200:69-77, 1997; a copy of which is attached) describes pHOG21 on Figure 1 (page 70-71, "Vector constructions"). These references further demonstrate that the term "pHOG21" specifically denotes a distinct plasmid, and that one skilled in the art by the disclosure of the present application would know that pHOG21 clearly and definitively describes a distinct plasmid. Therefore Claims 8 and 9 are clear and definite.

For the reasons above, the § 112, second paragraph rejection of Claims 1-9 should be withdrawn.

3. 35 U.S.C. § 112, first paragraph, enablement rejection.

The Examiner rejects Claims 8 and 9 under 35 U.S.C. § 112, first paragraph because allegedly "the pHOG21 vector is required to practice the claimed invention". Applicants traverse this rejection .

MPEP 2164.4 states:

> "In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1567, 27 USPQ2d 1510, 1513 (Fed. Cir.) 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure)."

The Examiner has not established a reasonable basis to question the enablement provided for Claims 8 and 9. The Examiner states that: "It is apparent that the pHOG21 vector is required to practice the claimed invention. As a required element, it must be known *and readily available to the public or obtainable by a repeatable method set forth in the specification.*" (page 6, lines 14-16; emphasis in the original). The Examiner has not stated that "the pHOG21 vector" is not enabled by the disclosure of the present application.

However, if the Examiner alleges that the pHOG21 vector is not enabled by the disclosure of the present application, then Applicants respectfully contend that the specification, when filed, contained sufficient information to enable one skilled in the art to make and use the invention, including the expression vector pHOG21. The specification discloses the individual components of plasmid pHOG21 in Figure 1 (page 4, line 32 to page 5, line 14), and that plasmid pHOG21 is also taught in Kiripyanov, et al. (*J. Immunol. Meth.* 196:51-62, 1996). Therefore, the specification enables the making and using of plasmid pHOG21.

For the reasons stated above, this 35 U.S.C. § 112, first paragraph rejection of Claims 8 and 9 should be withdrawn.

The Examiner rejects Claims 4-9 under 35 U.S.C. § 112, first paragraph because allegedly the specification does not enable "the desired mutation". Applicants avoid this rejection in that Claim 4 as amended does not recite "the desired mutation".

Therefore, this 35 U.S.C. § 112, first paragraph rejection of Claims 4-9 should be

withdrawn.

4. 35 U.S.C. § 102(b)

The Examiner rejects Claims 1-9 under 35 U.S.C. § 102(b) as being anticipated by Kipriyanov, et al. (*Protein Engineering* 10(4):445-53, 1997). The Applicants respectively traverse this rejection because Kipriyanov, et al. (1997) is not a prior art reference.

Applicants submit a correspondence from the Production Editor of the Oxford University Press indicating that the *Protein Engineering* Volume 10, No. 4, 1997 issue was dispatched on June 2, 1997. The priority date of the present application is May 23, 1997, which predates the date on which this reference was dispatched. Since the priority date of the present application (May 23, 1997) clearly predates the publication date of Kipriyanov, et al. (1997) (a date later than June 2, 1997), therefore **Kipriyanov, et al. (1997) is not a printed publication in this or a foreign country more than one year prior to the date of the present application**. Hence, Kipriyanov, et al. (1997) is not a prior art reference under 35 U.S.C. § 102(b).

For the reason stated above, the 35 U.S.C. § 102(b) rejection of Claims 1-9 over Kipriyanov, et al. (1997) should be withdrawn.

5. 35 U.S.C. § 103(a)

The Examiner rejects Claims 1-9 under 35 U.S.C. § 103(a) as being obvious over Kroon, et al. (*Pharmaceutical Res.* 9:1386-93, 1992) in view of Kipriyanov, et al (*J. Immunol. Meth.* 196:51-62, 1996) and in further view of Senoo, et al. (U.S. Patent No. 5,852,1767). Applicants respectively traverse the rejection of Claims 1-9 because Kroon, et al. in view of Kipriyanov, et al (1996) and in further view of Senoo, et al. do not render obvious Claims 1-9.

Kroon, et al. suggest that, among a considerable number of "candidate" amino acids, degradative changes in the cysteine of the third CDR of OKT3 may have a significant impact on the binding affinity of the antibody. However, Kroon, et al. neither disclose nor provide evidence that this is a primary event responsible for the instability of OKT3 at low or high temperatures. For example, extensive deamidations of several asparagine residues were found and five methionine residues were oxidized. These degradative changes were found both in

the constant domains and in the antibody variable domains. It is a well known fact to a person skilled in the art that the mutation of only one amino acid can potentially alter the structure of a protein. Particularly critical amino acids can be recognized by the fact that they have remained unchanged during evolution. Kroon, et al., for example, point out in the last paragraph that the conserved residue Ans386 may be a source of instability in other antibodies. Whereas changes in the structure of a protein through the degradation of one or more amino acids may perhaps lead to a more exposed position of oxidation-susceptible amino acids such as methionine and cysteine, however, Kroon, et al. do not disclose whether any one amino acid can be responsible for such instability. Thus, whereas Kroon, et al. disclose that several amino acids are subject to degradation an storage of OKT3, it is not obvious to one skilled in the art which one amino acid can be primarily responsible for the instability.

Senoo, et al. showed that the substitution of one or more particular cysteines by serine improved the stability of basic fibroblast growth factor under acidic conditions. However, this is a completely different protein to OKT3. It can be substantially mutated without losing activity. For example, as many as 46 amino acid residues were deleted in a preferred mutant of this protein. Radic, et al. (*Methods* 11:20-26, 1997; a copy of which is attached) show that changing a single amino acid of an anti dsDNA antibody (R53 of VH3H9) can completely eliminate binding (see page 20, "Abstract"). In the present case, the mutated cysteine in OKT3 is situated in the center of the CDR3 domain of the variable heavy chain domain, which many structural studies have shown to play a major role in antigen binding. Even minor changes in this region would be expected to have a profound affect on the antibody binding activity.

Thus is no reasonable expectation of success that substituting the cysteine of the V_H domain of the OKT3 antibody at position H100A, according to the Kabat numbering system, with a polar amino acid would increase its stability at antibody binding but that it still binds antigen with no appreciable loss if binding activity.

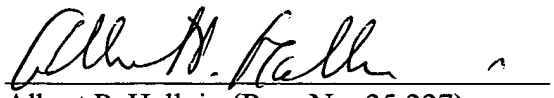
For the reasons stated above, the 35 U.S.C. § 103(a) rejection of Claims 1-9 over Kroon, et al. in view of Kipriyanov, et al (1996) and in further view of Senoo, et al. should be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, the Applicants believe the application is in good and proper condition for allowance. Early notification of allowance is earnestly solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 463-8109. A telephone conference is especially requested if the Examiner intends to maintain the present rejections.

Respectfully submitted,

Date: December 20, 2001



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MARKED-UP VERSION OF THE REPLACEMENT PARAGRAPHS AND CLAIMS

In the Specification

On page 1, after "Mutated OKT3 Antibody", insert:

--**CROSS-REFERENCE TO RELATED APPLICATIONS**

The present application is a National Stage of International Application No. PCT/DE98/01409, filed May 22, 1998, which claims priority to German Patent Application No. 197 21 700.1, filed May 23, 1997.--

On page 1, lines 14-15, delete "12301 Parklawn Drive, Rockville, MD 20852" and insert --10801 University Boulevard, Manassas, VA 20110-2209--.

On page 6, line 18, after "5'-GTAGTCAAGGCTGTAATGATCATC" insert --(SEQ ID NO: 7)--.

In the Claims

Please amend Claims 1-4 and 6-9, and add new Claims 12-23; as follows:

1. (Amended) A [monoclonal] recombinant antibody product , [characterized by an exchange of] comprising the V_H domain of the OKT3 antibody, wherein the cysteine [for another polar amino acid] at position H100A [the OKT3 antibody known under this name] of said V_H domain is substituted with a polar amino acid , wherein said position H100A is according to the Kabat numbering system .

2. (Amended) The [monoclonal] recombinant antibody product , characterized in that the polar amino acid is serine.

3. (Amended) The [monoclonal] recombinant antibody product according to claim 1[or 2, characterized in that it includes the sequence indicated in figure 2] comprising the amino acid sequence depicted by SEQ ID NO: 2 .

4. (Amended) A method for the production of the [monoclonal] recombinant antibody product according to any one of claims 1 to 3, characterized by the steps of:

a) [obtainment of] obtaining mRNA from freshly subcloned hybridoma cells of OKT3 and transcription into cDNA,

b) [amplification of] amplifying the DNA coding for the variable domains of the light and heavy chains by means of PCR [using suitable primers] ,

c) cloning of the DNA obtained in b) into a vector adapted for site-specific mutagenesis as well as introduction of [the desired mutation using suitable primers,] a mutation in said position H100A of the V_H domain, wherein said position H100A is according to the Kabat numbering system, wherein said mutation is the substitution of a cysteine with a polar amino acid, and

d) [insertion of] inserting the mutated DNA obtained in c) in an expression vector and expression in a suitable expression system.

5. (Reiterated) The method according to claim 4, wherein the primers used in step b) are Bi5, Bi8, Bi4 and Bi3f.

6. (Amended) The method according to claim 4 [or 5], wherein the vector used in step c) is pCR-Skript SK(+).

7. (Amended) The method according to [any one of claims 4 to 6] claim 4 , wherein [the primer SK1 5'-GTAGTCAAGGCTGTAATGATCATC is used in step c)] said cloning uses a primer comprising the sequence depicted by SEQ ID NO: 7 .

8. (Amended) The method according to [any one of claims 4 to 7] claim 4 , wherein the expression vector used in step d) is pHOG21.

9. (Amended) The method according to [any one of claims 4 to 8] claim 4 , wherein the expression takes place in XLl-Blue E. *coli* cells.

Please the following new claims:

--12. (New) The method according to claim 5, wherein the vector used in step c) is pCR-Skript SK(+).

13. (New) The method according to claim 5, wherein said cloning uses a primer comprising the sequence depicted by SEQ ID NO: 7.

14. (New) The method according to claim 6, wherein said cloning uses a primer comprising the sequence depicted by SEQ ID NO: 7.

15. (New) The method according to claim 5, wherein the expression vector used in step d) is pHOG21.

16. (New) The method according to claim 6, wherein the expression vector used in step d) is pHOG21.

17. (New) The method according to claim 7, wherein the expression vector used in step d) is pHOG21.

18. (New) The method according to claim 4, wherein the expression takes place in XL1-Blue E. *coli* cells.

19. (New) The method according to claim 5, wherein the expression takes place in XL1-Blue E. *coli* cells.

20. (New) The method according to claim 6, wherein the expression takes place in XL1-Blue E. *coli* cells.

21. (New) The method according to claim 7, wherein the expression takes place in XL1-

Blue E. *coli* cells.

22. (New) The method according to claim 8, wherein the expression takes place in XLl-Blue E. *coli* cells.

23. (New) A peptide comprising the amino acid sequence depicted by SEQ ID NO: 2.

24. (New) An antibody comprising the peptide according to Claim 23.

25. (New) A single-chain antibody comprising the peptide according to Claim 23.

26. (New) A bispecific antibody comprising the peptide according to Claim 23.

27. (New) A recombinant antibody product comprising the peptide according to Claim 23.--